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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/070436
INTERNATIONAL APPLICATION NO. PCT/JP00/06398	INTERNATIONAL FILING DATE 20 September 2000	PRIORITY DATE CLAIMED 20 September 1999

TITLE OF INVENTION

PROCESS FOR THE PREPARATION OF CYCLIC LACTIC ACID OLIGOMERS

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information

1. X This is a FIRST submission of items concerning a filing under 35 U.S.C. 371
2. ___ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. X This is an express request to promptly begin national examination procedures (35 U S C 371(f)).
4. X The US has been elected by the expiration of 19 months from the priority date (PCT Article 31)
5. X A copy of the International Application as filed (35 U S C 371(c)(2))
   a. X is attached hereto (required only if not communicated by the International Bureau).
   b. X has been communicated by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. X An English language translation of the International Application as filed (35 U.S.C 371 (c)(2))
7. X Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C 371(c)(3))
   a. ___ are attached hereto (required only if not communicated by the International Bureau)
   b. ___ have been communicated by the International Bureau
   c. ___ have not been made, however, the time limit for making such amendments has NOT expired.
   d. X have not been made and will not be made.
8. ___ An English language translation of the amendments to the claims under PCT Article 19 (35 U S C 371(c)(3))
9. X An oath or declaration of the inventor(s) (35 U.S.C .371(c)(4))
   "UNEXECUTED"
10. X An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (U.S.C. 371(c)(5)).

Items 11 to 16 below concern other document(s) or information included:

11. Assignee: AMATO PHARMACEUTICAL PRODUCTS, LTD., of Kyoto, JAPAN
12. ___ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ___ An assignment document for recording A separate cover sheet in compliance with 37 CFR 3 28 and 3.31 is included.
14. X A FIRST preliminary amendment.
    ___ A SECOND or SUBSEQUENT preliminary amendment
15. ___ A substitute specification
16. ___ A change of power of attorney and/or address letter
17. X Figure of Drawing to be published 1
18. X Other items or information:

    International Application as published in Japanese
    Cover Letter under 35 U S.C. 371 AND 37 C.F.R. 1.495.
    PCT/IPEA/409 International Preliminary Examination Report.
    PCT/ISA/210 (in English & Japanese).
    PCT/IB/301.
    PCT/IB/304
    PCT/IB/308
    PCT/IB/332
    PCT/IB/338.
    PCT/IPEA/408 Written Opinion.
    PCT/IB/306
    PCT/RO/101 PCT REQUEST (with International Application as filed in Japanese).
    Claim of Priority

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/070436	PCT/JP00/06398	P22118

19. X The following fees are submitted.	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)).		
Search report has been prepared by the EPO or JPO . . . . . $ 890 00		
International preliminary examination fee paid to USPTO (37 CFR 1 482) . . . . . $ 710 00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO(37 CFR 1.445(a)(2) . . . . . $ 740 00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO. $1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). . . . . .$ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890 00	
Surcharge of $130.00 for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0 00	

Claims	Number Filed		Number Extra	RATE		
Total Claims	9	- 20 =	0	X $18.00	$ 0.00	
Independent Claims	1	- 3 =	0	X $84.00	$ 0 00	
Multiple dependent claim(s) (if applicable)				+ $280.00	$ 0 00	
TOTAL OF ABOVE CALCULATIONS =					$890 00	
___ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.					$ 0.00	
SUBTOTAL =					890 00	
Processing fee of $130 00 for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					0.00	
Extension of Time fee in the amount of $					0.00	
TOTAL NATIONAL FEE =					890.00	
Fee for recording the enclosed assignment (37 CFR 1 21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 00 per property +					0 00	
TOTAL FEES ENCLOSED =					890.00	
Amount to be refunded					$	
Charged					$	

a. X A check in the amount of $890.00 to cover the above fees is enclosed.

b. ___ Please charge my Deposit Account No _____ in the amount of $_____ to cover the above fees.

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No 19-0089.

NOTE: Where an appropriate time limit under 37 CFR 1 494 or 1.495 has not been met, a petition to revive (37 CFR 1 137(a) or (b)) must be filed and granted to restore the application to pending status

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29,027
REGISTRATION NUMBER

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mikio WATANABE et al.

Serial No : Not Yet Assigned (National Stage of PCT/JP00/006398)

Filed : Concurrently Herewith (International Filing Date 20 September 2000)

For : METHOD FOR PRODUCING CYCLIC LACTIC ACID OLIGOMER

PRELIMINARY AMENDMENT

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to calculation of the filing fees and the examination of the above-identified patent application on the merits, the Examiner is respectfully requested to amend the claims as follows:

IN THE CLAIMS

Please amend claims 3-6 and 8, as follows (a marked-up copy of the amendment is provided in the attached Appendix):

3. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein said alkali metal compound is a compound of formula (2) wherein Y is -O- or -S-.

4. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein said alkali metal compound is a compound of formula (2) wherein Me is lithium.

5. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein in formula (1), m is an integer of 1 to 21.

6. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein said alkali metal compound is any of:
a compound of formula (2) wherein R is an aliphatic group having 4 or more carbon atoms, a compound of formula (2) wherein R is an aromatic group and Y is -S-; or a compound of formula (2) wherein R is $-CH(R^{20})CONR^{21}R^{22}$ wherein R^{20} represents an aliphatic group and of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group.

8. (Amended) A cyclic lactic acid oligomer, which is produced by the method for producing a cyclic lactic acid oligomer according to claim 1.

P22118.A01

REMARKS

By the above amendment, claims 3-6 and 8 have been amended to delete multiple dependency.

If there should be any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,
Mikio WATANABE et al.

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P22118.A01

APPENDIX
MARKED-UP COPY OF CLAIM AMENDMENTS

3. (Amended) The method for producing a cyclic lactic acid oligomer according to [claim 1 or 2] claim 1, wherein said alkali metal compound is a compound of formula (2) wherein Y is -O- or -S-.

4. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 3] claim 1, wherein said alkali metal compound is a compound of formula (2) wherein Me is lithium.

5. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 4] claim 1, wherein in formula (1), m is an integer of 1 to 21.

6. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 5] claim 1, wherein said alkali metal compound is any of: a compound of formula (2) wherein R is an aliphatic group having 4 or more carbon atoms, a compound of formula (2) wherein R is an aromatic group and Y is -S-; or a compound of formula (2) wherein R is $-CH(R^{20})CONR^{21}R^{22}$ wherein R^{20} represents an aliphatic group and of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group.

8. (Amended) A cyclic lactic acid oligomer, which is produced by the method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 7] claim 1.

31/PRTS

DESCRIPTION

METHOD FOR PRODUCING CYCLIC LACTIC ACID OLIGOMER

TECHNICAL FIELD

The present invention relates to a method for producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the production method.

BACKGROUND ART

A lactic acid oligomer having a cyclic structure is a useful compound which is used as a medicament such as a tumor cell growth inhibiting agent (Japanese Patent Application Laying-Open (Kokai) No. 3-193731) or an antineoplastic agent (Japanese Patent Application Laying-Open (Kokai) No. 9-227388), or an intermediate thereof.

The conventional method for producing such a lactic acid oligomer involves subjecting lactic acids to dehydration condensation by heating under an inactive atmosphere, and then separating and collecting an oligomer component from the obtained reaction products.

However, since it is difficult to produce a lactic acid oligomer selectively by this conventional method and that the lactic acid polymer obtained in the dehydration condensation process of lactic acids has a broad molecular weight distribution, containing high polymers, it is necessary to separate and collect a lactic acid oligomer by separation means such as chromatography.

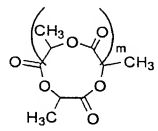
DISCLOSURE OF THE INVENTION

The object of the present invention is to provide a novel method for effectively producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the method.

As a result of concentrated research to achieve the aforementioned object, the present inventors have found that a cyclic lactic acid oligomer can be produced effectively by polymerization of lactides in the presence of a certain alkali metal

compound, thereby providing the present invention.

Thus, according to the present invention, there is provided a method for producing a cyclic lactic acid oligomer represented by the following formula (1):



(1)

wherein m represents an integer of 1 to 30,

wherein lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein R represents an aliphatic group, aromatic group, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;

Y represents –O-, -S- or $-NR^{40}$-, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and

Me represents an alkali metal.

Preferably, the alkali metal compound is a compound of formula (2) wherein R represents an alkyl group having 1 to 12 carbon atoms, aryl group having 6 to 30 carbon atoms, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group.

Preferably, the alkali metal compound is a compound of formula (2) wherein

Y is –O- or –S-.

Preferably, the alkali metal compound is a compound of formula (2) wherein Me is lithium.

Preferably, in formula (1), m is an integer of 1 to 21.

According to one embodiment of the present invention, as the alkali metal compound, there is used any of: a compound of formula (2) wherein R is an aliphatic group having 4 or more carbon atoms; a compound of formula (2) wherein R is an aromatic group and Y is –S-; or a compound of formula (2) wherein R is $-CH(R^{20})CONR^{21}R^{22}$ wherein R^{20} represents an aliphatic group and each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group. In the case of using such alkali metal compounds, cyclic lactic acid oligomer is selectively produced substantially free of chain lactic acid oligomer.

According to another aspect of the present invention, there is provided a cyclic lactic acid oligomer, which is produced by the aforementioned method for producing a cyclic lactic acid oligomer according to the present invention. Preferably, there is provided the cyclic lactic acid oligomer which is substantially free of chain lactic acid oligomer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a general view of NMR of the product obtained in Example 1.

Figure 2 shows a partial scale view of NMR of Figure 1.

Figure 3 shows a partial scale view of NMR of Figure 1.

Figure 4 shows a general view of NMR of the product obtained in Example 2.

Figure 5 shows a partial scale view of NMR of Figure 4.

Figure 6 shows a partial scale view of NMR of Figure 4.

Figure 7 shows a general view of NMR of the product obtained in Example 3.

Figure 8 shows a partial scale view of NMR of Figure 7.

Figure 9 shows a partial scale view of NMR of Figure 7.

Figure 10 shows an MS spectrum of the product obtained in Example 4.

Figure 11 shows a general view of NMR of the product obtained in Example 4.

Figure 12 shows a partial scale view of NMR of Figure 11.

Figure 13 shows a partial scale view of NMR of Figure 11.

Figure 14 shows a general view of NMR of the product obtained in Example 5.

Figure 15 shows a partial scale view of NMR of Figure 14.

Figure 16 shows a partial scale view of NMR of Figure 14.

Figure 17 shows a general view of NMR of the product obtained in Example 6.

Figure 18 shows a partial scale view of NMR of Figure 17.

Figure 19 shows a partial scale view of NMR of Figure 17.

Figure 20 shows a general view of NMR of the product obtained in Example 7.

Figure 21 shows a partial scale view of NMR of Figure 20.

Figure 22 shows a partial scale view of NMR of Figure 20.

Figure 23 shows a general view of NMR of the product obtained in Example 8.

Figure 24 shows a partial scale view of NMR of Figure 23.

Figure 25 shows a partial scale view of NMR of Figure 23.

Figure 26 shows a general view of NMR of the product obtained in Example 9.

Figure 27 shows a partial scale view of NMR of Figure 26.

Figure 28 shows an MS spectrum of the product obtained in Example 10.

Figure 29 shows a general view of NMR of the product obtained in Example 10.

Figure 30 shows a partial scale view of NMR of Figure 29.

Figure 31 shows a partial scale view of NMR of Figure 29.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The embodiments and methods for carrying out the present invention are described in detail below.

The method for producing a cyclic lactic acid oligomer of the present invention is characterized in that lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein R represents an aliphatic group, aromatic group, -Si(R^{10})(R^{11})(R^{12}), -CH(R^{20}) $CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;

Y represents -O-, -S- or $-NR^{40}$-, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and

Me represents an alkali metal.

The raw material in the production method of the present invention is lactide (3,6-dimethyl-1,4-dioxane-2,5-dione) obtained by condensation of two molecules of lactic acid by dehydration, and this lactide is reacted in the presence of the alkali metal compound represented by the above-mentioned formula (2). The formula (2):

R-Y-Me (2)

is described below.

In formula (2), R represents an aliphatic group, aromatic group, -Si(R^{10})(R^{11})(R^{12}), -CH(R^{20}) $CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group.

The aliphatic group in the present specification may be a straight chain, branched chain, cyclic, or combined thereof, and may be saturated or unsaturated aliphatic hydrocarbon group having 1 to 12, preferably 1 to 6 carbon atoms. Examples thereof include alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, octyl and dodecyl, and cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclooctyl and cyclododecyl. The aliphatic group may be an unsaturated hydrocarbon group having a double or triple bond.

The aromatic group in the present invention may be an aryl group and an arylalkyl group having 6 to 30, preferably 6 to 20, more preferably 6 to 12, and further more preferably 6 to 10 carbon atoms. Examples of the aryl group include phenyl, tolyl and naphthyl, and examples of the arylalkyl group include benzyl, phenethyl and naphthylmethyl.

The aliphatic group and the aromatic group may have one or more substituent(s). The type of substituents is not particularly limited, and examples include a straight chain, branched chain or cyclic alkyl group, a straight chain, branched chain or cyclic alkenyl group, a straight chain, branched chain or cyclic alkynyl group, an aryl group, an acyloxy group, an alkoxycarbonyloxy group, an aryloxycarbonyloxy group, a carbamoyloxy group, a carbonamide group, a sulfonamide group, a carbamoyl group, a sulfamoyl group, an alkoxy group, an aryloxy group, an aryloxycarbonyl group, an alkoxycarbonyl group, an N-acylsulfamoyl group, an N-sulfamoylcarbamoyl group, an alkylsulfonyl group, an arylsulfonyl group, an alkoxycarbonylamino group, an aryloxycarbonylamino group, an amino group, an ammonio group, a cyano group, a nitro group, a carboxyl group, a hydroxyl group, a sulfo group, a mercapto group, an alkylsulfinyl group, an arylsulfinyl group, an alkylthio group, an arylthio group, an ureide group, a heterocyclic group (e.g. a monocyclic or condensed ring containing at least one or more nitrogen, oxygen or sulfur atom(s) and consisting of 3 to 12 ring forming members), a heterocyclic oxy group, a heterocyclic thio group, an acyl group, a sulfamoylamino group, a silyl group, and a halogen atom. In the above description, the carbon number of alkyl, alkenyl, alkynyl and alkoxy is generally 1 to 12, preferably 1 to 6, and the carbon number of aryl is generally 6 to 20, preferably 6 to 10.

In formula (2), Y represents –O-, -S- or $-NR^{40}-$, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group. Preferably, Y is –O- or -S-. Examples of aliphatic or aromatic groups represented by R^{40} are as stated above.

In formula (2), Me represents an alkali metal. Examples of alkali metal include Li, Na or K, and Li is preferable.

Among compounds represented by formula (2), the compounds having

asymmetric carbon atoms may be any one of (R) form, (S) form, and (R),(S) form.

A method for obtaining an alkali metal compound represented by formula (2) is not particularly limited, and a person skilled in the art can obtain the compound as appropriate. For example, the alkali metal compound can be obtained by reaction of R-YH with an alkylated alkali metal such as n-butyllithium.

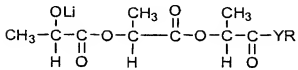
Where lactides are polymerized in the presence of an alkali metal compound represented by formula (2) according to the method of the present invention, the amount of alkali metal compound (R-Y-Me) is preferably 0.1 to 1 mole, more preferably 0.2 to 0.3 mole per mole of lactide.

When the method of the present invention is carried out, the reaction temperature is not particularly limited as long as the reaction progresses, and the reaction temperature is preferably -100°C to room temperature, more preferably -78°C to -50°C. It is preferable that the reaction is initiated at a temperature of -78°C to -50°C and that the reaction is performed while gradually raising the temperature to room temperature.

Polymerization reaction of lactides in the method of the present invention is preferably carried out in the presence of a reaction solvent. The reaction solvent is not particularly limited as long as it is inactive for the reaction, and examples of preferred solvents include cyclic ether such as tetrahydrofuran, diethylether, and dimethoxyethane. Examples of reaction atmospheres may be inactive gas atmospheres such as nitrogen gas and argon gas. Reaction pressure is not particularly limited, and is preferably normal pressure.

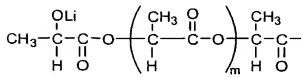
Next, the reaction mechanism of production of a cyclic lactic acid oligomer by the method of the present invention is described, but the following theory is not intended to limit the scope of the present invention. The case of using Li as an alkali metal compound is described herein, but it is considered that the reaction mechanism is similar where other alkali metal compounds such as Na or K are used. In the polymerization reaction of lactides in the method of the present invention, first, a lithium compound and lactide are reacted to generate a chain lactic acid derivative

represented by the following formula (4):



(4)

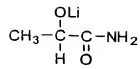
wherein Y and R are as defined above in the present specification. Then, lactide is reacted with this compound to generate a chain lactic acid oligomer represented by the following formula (5):



(5)

wherein m, Y and R are as defined above in the present specification. Subsequently, RYLi is removed from this compound, and the compound is cyclized, so that a cyclic lactic acid oligomer of the above formula (1) is considered to be generated.

The composition of a lactic acid oligomer obtained by the method of the present invention is changed depending on an alkali metal compound used as a reaction assistant. For example where the alkali metal compound (preferably a lithium compound) of alkyl alcohol having 1 to 3 carbon atoms is used, a mixture (the ratio of cyclic lactic acid oligomer : 80 to 85% by weight) of a cyclic lactic acid oligomer and a chain oligomer can be obtained. In contrast, where the alkali metal compound of alkyl alcohol having 4 or more carbon atoms such as t-butyl alcohol, or the alkali metal compound of thiophenol and the like, is used, substantially only cyclic lactic acid oligomer can be obtained selectively. Also, substantially only cyclic lactic acid oligomer can be obtained selectively by using, as an alkali metal compound, a compound of formula (2) wherein R is $-CH(R^{20})\ CONR^{21}R^{22}$, wherein R^{20} is an aliphatic group and each of R^{21} and R^{22} is independently a hydrogen atom, aliphatic group or an aromatic group, more specifically, for example, lactic acid amide represented by the following formula (3):

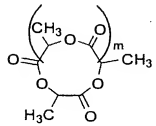


(3)

The term "substantially only cyclic lactic acid oligomer is obtained selectively" is used in the present specification to mean that substantially no chain lactic acid oligomers are generated in a reaction product, and specifically it means that the ratio of chain lactic acid oligomer to total lactic acid oligomer in a reaction product is generally 10% by weight or less, preferably 5% by weight or less, and particularly preferably 3% by weight or less.

As stated above, one advantage of the present invention is that the composition of a cyclic lactic acid oligomer and a chain oligomer in a reaction product can be controlled by selection of the type of an alkali metal compound.

According to the method of the present invention, there is produced a cyclic lactic acid oligomer represented by the following formula (1):



(1)

In formula (1), m represents an integer of 1 to 30, preferably 1 to 21.

The reaction product obtained by the method of the present invention is generally a mixture of cyclic lactic acid oligomers, wherein m represents an integer of 1 to 30, for example, 1 to 28, 1 to 25, 1 to 21, or 1 to 19.

The present invention also relates to a cyclic lactic acid oligomer, which is produced by the aforementioned method for producing a cyclic lactic acid oligomer of the present invention. In a preferred embodiment for the present invention, a mixture of cyclic lactic acid oligomers substantially free of chain lactic acid oligomers can be

produced.

The mixture of cyclic lactic acid oligomers produced by the method of the present invention (or a single substance obtained by purification from the mixture) is useful as a tumor cell growth inhibiting agent, an antineoplastic agent, a preventive agent against cancer metastasis, a QOL improving agent for cancer patients, an immune activating agent, and the like, and the mixture can also be used for prevention and/or treatment of diabetes or diabetes complications since it has an action of reducing blood sugar level. Moreover, the mixture of cyclic lactic acid oligomers produced by the method of the present invention (or a single substance obtained by purification from the mixture) has an action of repressing excessive appetite and promoting basal metabolism, and so it can be used also as a medicament useful for improvement and/or prevention of adiposis and enhancement of effects of kinesitherapy, and is also useful as an agent for promoting glycogen accumulation or an agent for enhancing physical fitness. Furthermore, a cyclic lactic acid oligomer produced by the method of the present invention is useful not only as a medicament, but also as health foods or diet supplements including beverages, which is generally called soft drinks, drinkable preparations, health foods, specific hygienic foods, functional foods, function activating foods, nutritional supplementary foods, supplements, feed, feed additives, and the like.

The present invention is further described in the following examples. It is apparent to those skilled in the art that materials, usage, proportion, treatment, treatment process and the like shown in the following examples can be modified as appropriate, as long as the modifications are within the spirit and scope of the invention, and the examples are not intended to limit the scope of the invention.

EXAMPLES

Example 1

A THF solution (2ml) in which 0.033g (1.03mmol) of methanol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of

n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 4 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.551g (yield 90.5%) of product consisting of a mixture of cyclic oligo-lactate and chain oligo-lactate was obtained with a weight ratio between cyclic oligomer and chain oligomer being 84 : 16.

A general view of NMR of the product obtained in Example 1 is shown in Figure 1, and scale views of a part of Figure 1 are shown in Figures 2 and 3.

Example 2

A THF solution (2ml) in which 0.054g (1.17mmol) of ethanol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred for 30 minutes.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere and 10ml of water was further added thereto, and then the temperature was raised to room temperature by removal of the dry ice/acetone bath. Subsequently, the mixture was extracted with 20ml of ether 8 times, and the ether layer was washed with 30ml of saturated saline solution. Then,

anhydrous sodium sulfate was added thereto and dried while stirring for 1 hour. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.535g (yield 84.9%) of product consisting of a mixture of cyclic oligo-lactate and chain oligo-lactate was obtained with a weight ratio between cyclic oligomer and chain oligomer being 82:18.

A general view of NMR of the product obtained in Example 2 is shown in Figure 4 and scale views of a part of Figure 4 are shown in Figures 5 and 6.

Example 3

A THF solution (2ml) in which 0.062g (1.03mmol) of 2-propanol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred , and the temperature was gradually raised to room temperature over 4 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.589g (yield 92.3%) of product consisting of a mixture of cyclic oligo-lactate and chain oligo-lactate was obtained with a weight ratio between cyclic oligomer and chain oligomer being 80 : 20.

A general view of NMR of the product obtained in Example 3 is shown in Figure 7, and scale views of a part of Figure 7 are shown in Figures 8 and 9.

Example 4

A THF solution (2ml) in which 0.074g (1.00mmol) of tert-butanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

An MS spectrum of the product obtained in Example 4 is shown in Figure 10. In addition, a general view of NMR of the product obtained in Example 4 is shown in Figure 11, and scale views of a part of Figure 11 are shown in Figures 12 and 13.

Example 5

A THF solution (2ml) in which 0.117g (1.06mmol) of thiophenol was dissolved was added to a 50ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to -78°C in a dry ice/acetone bath. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.576g (4.00mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane-2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 4 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further

added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.612g (yield 88.3%) of product was obtained. It was confirmed by NMR analysis that this product comprised cyclic oligo-lactate and chain oligo-lactate at a weight ratio of 96 : 4.

0.238g of the product was isolated and purified using silica gel chromatography (solvent; hexane : ether = 1 : 2) to obtain 5 fractions (fraction Nos. 10-1 to 10-5).

A general view of NMR of the product obtained in Example 5 is shown in Figure 14, and scale views of a part of Figure 14 are shown in Figures 15 and 16.

Example 6

3ml of THF solution containing 0.089g (1mmol) of S-lactic acid amide was added to a 50ml double-cap eggplant-shaped flask at room temperature under a nitrogen atmosphere, and 0.64ml (1.00mmol) of n-butyllithium was reacted therewith at -78°C followed by stirring for 15 minutes. Further, 2ml of THF solution containing 0.576g (4mmol) of L-(-)-lactide was added thereto and reacted therewith for 30 minutes, and then the temperature was raised from -78°C to 0°C followed by reaction for 1.5 hours. Subsequently, the temperature was further raised to room temperature by addition of 5ml of saturated ammonium chloride solution. After the mixture was extracted with chloroform, the organic layer was washed with a saturated saline solution, and dried with anhydrous sodium sulfate followed by vacuum concentration (NMR sa0140), to obtain a residue.

A general view of NMR of the product obtained in Example 6 is shown in Figure 17, and scale views of a part of Figure 17 are shown in Figures 18 and 19.

Example 7

A THF solution (2ml) in which 0.090g (1.00mmol) of trimethylsilanol was

dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to 0°C. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane -2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

A general view of NMR of the product obtained in Example 7 is shown in Figure 20, and scale views of a part of Figure 20 are shown in Figures 21 and 22.

Example 8

A THF solution (2ml) in which 0.276g (1.00mmol) of triphenylsilanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to 0°C. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane -2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried

overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

A general view of NMR of the product obtained in Example 8 is shown in Figure 23, and scale views of a part of Figure 23 are shown in Figures 24 and 25.

Example 9

A THF solution (2ml) in which 0.132g (1.00mmol) of t-butyldimethylsilanol was dissolved was added to a 25ml double-cap eggplant-shaped flask under a nitrogen atmosphere, and cooled to 0°C. Then, 0.64ml (1.00mmol) of n-butyllithium was added thereto and the mixture was stirred for 15 minutes. Further, a THF solution (2ml) in which 0.434g (3.01mmol) of (3R,6R)-(+)-3,6-dimethyl-1,4-dioxane -2,5-dione was dissolved was added thereto and stirred, and the temperature was gradually raised to room temperature over 2.5 hours.

After completion of stirring, 2ml of saturated ammonium chloride was added to the mixture while maintaining a nitrogen atmosphere, and 10ml of water was further added thereto. The mixture was extracted with chloroform and a saturated saline solution and washed, and then anhydrous sodium sulfate was added thereto and dried overnight. The obtained product was subjected to vacuum concentration in which solvent was completely removed with a vacuum pump. As a result, 0.537g (yield 82.5%) of cyclic oligo-lactate wherein all asymmetric carbon atoms have an R configuration, was obtained.

A general view of NMR of the product obtained by Example 9 is shown in Figure 26, and a scale view of a part of Figure 26 is shown in Figure 27.

Example 10

3ml of THF solution containing 0.118g (1mmol) of ethyl S-lactate was added to a 50ml double-cap eggplant-shaped flask at room temperature under a nitrogen

atmosphere, and 0.64ml (1.00mmol) of n-butyllithium was reacted therewith at -78°C followed by stirring for 15 minutes. Further, 2ml of THF solution containing 0.576g (4mmol) of L-(-)-lactide was added thereto and reacted therewith for 30 minutes, and then the temperature was raised from -78°C to 0°C followed by reaction for 1.5 hours. Subsequently, the temperature was further raised to room temperature by addition of 5ml of saturated ammonium chloride solution. After the mixture was extracted with chloroform, the organic layer was washed with a saturated saline solution, and dried with anhydrous sodium sulfate followed by vacuum concentration (NMR sa0140), to obtain the residue.

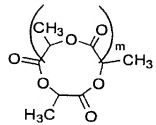
An MS spectrum of the product obtained in Example 10 is shown in Figure 28. In addition, a general view of NMR of the product obtained in Example 10 is shown in Figure 29, and scale views of a part of Figure 29 are shown in Figures 30 and 31.

INDUSTRIAL APPLICABILITY

According to the method for producing a cyclic lactic acid oligomer of the present invention, a cyclic lactic acid oligomer can be produced at good yield, and its industrial significance is great. In addition, a cyclic lactic acid oligomer produced by the production method of the present invention is useful as a tumor cell growth inhibiting agent, antineoplastic agent, preventive agent against cancer metastasis, QOL improving agent for cancer patients, immune activating agent, therapeutic agent for diabetes, antiobestic agent, an agent for promoting glycogen accumulation or an agent for enhancing physical fitness. Furthermore, the cyclic lactic acid oligomer is useful not only as a medicament, but also as various types of health foods and diet supplements including soft drinks, drinkable preparations, health foods, specific hygienic foods, functional foods, function activating food, nutritional supplementary foods, supplements, feed, feed additives, and the like.

CLAIMS

1. A method for producing a cyclic lactic acid oligomer represented by the following formula (1):



(1)

wherein m represents an integer of 1 to 30,

wherein lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein R represents an aliphatic group, aromatic group, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;

Y represents $-O-$, $-S-$ or $-NR^{40}-$, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and

Me represents an alkali metal.

2. The method for producing a cyclic lactic acid oligomer according to claim 1, wherein said alkali metal compound is a compound of formula (2) wherein R represents an alkyl group having 1 to 12 carbon atoms, aryl group having 6 to 30 carbon atoms, $-Si(R^{10})(R^{11})(R^{12})$, $-CH(R^{20})CONR^{21}R^{22}$ or $-CH(R^{30})COOR^{31}$, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom,

aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group.

3. The method for producing a cyclic lactic acid oligomer according to claim 1 or 2, wherein said alkali metal compound is a compound of formula (2) wherein Y is –O- or –S-.

4. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 3, wherein said alkali metal compound is a compound of formula (2) wherein Me is lithium.

5. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 4, wherein, in formula (1), m is an integer of 1 to 21.

6. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 5, wherein said alkali metal compound is any of:
a compound of formula (2) wherein R is an aliphatic group having 4 or more carbon atoms; a compound of formula (2) wherein R is an aromatic group and Y is –S-; or a compound of formula (2) wherein R is $-CH(R^{20})CONR^{21}R^{22}$ wherein R^{20} represents an aliphatic group and each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group.

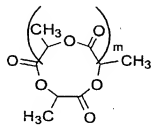
7. The method for producing a cyclic lactic acid oligomer according to claim 6, wherein cyclic lactic acid oligomer is selectively produced substantially free of chain lactic acid oligomer.

8. A cyclic lactic acid oligomer, which is produced by the method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 7.

9. The cyclic lactic acid oligomer according to claim 8, which is substantially free of chain lactic acid oligomer.

ABSTRACT

The object of the present invention is to provide a novel method for effectively producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the method. According to the present invention, there is provided a method for producing a cyclic lactic acid oligomer represented by the following formula (1):



(1)

wherein m represents an integer of 1 to 30,

wherein lactides are polymerized in the presence of an alkali metal compound represented by the following formula (2):

R-Y-Me (2)

wherein R represents an aliphatic group, aromatic group, -Si(R^{10})(R^{11})(R^{12}), -CH(R^{20})CONH$R^{21}R^{22}$ or –CH(R^{30})COOR^{31}, wherein each of R^{10}, R^{11} and R^{12} independently represents an aliphatic or aromatic group, R^{20} represents an aliphatic group, each of R^{21} and R^{22} independently represents a hydrogen atom, aliphatic group or aromatic group, R^{30} represents an aliphatic group, and R^{31} represents a hydrogen atom, aliphatic group or aromatic group;

Y represents –O-, -S- or –NR^{40}-, wherein R^{40} represents a hydrogen atom, aliphatic group or aromatic group; and

Me represents an alkali metal; and,

a cyclic lactic acid oligomer produced by the above production method.

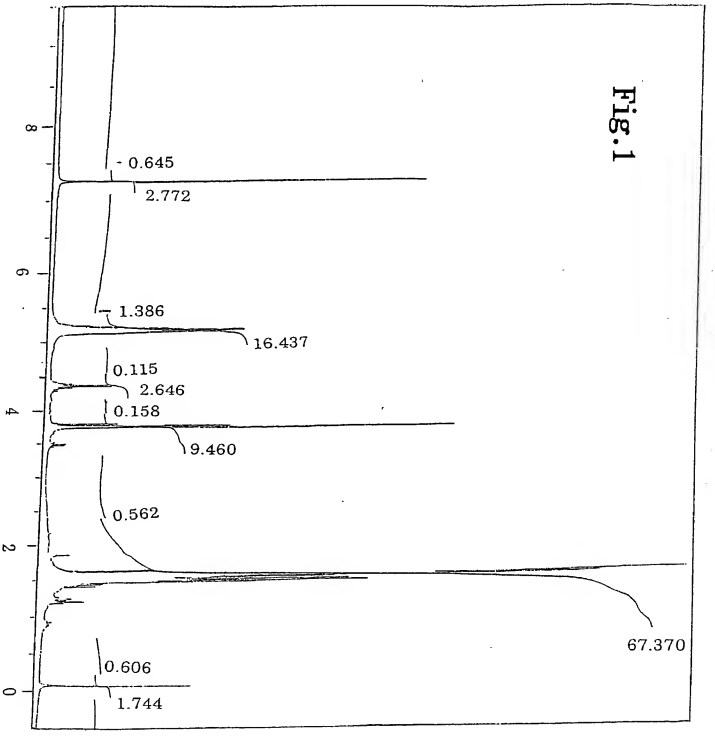


Fig.1

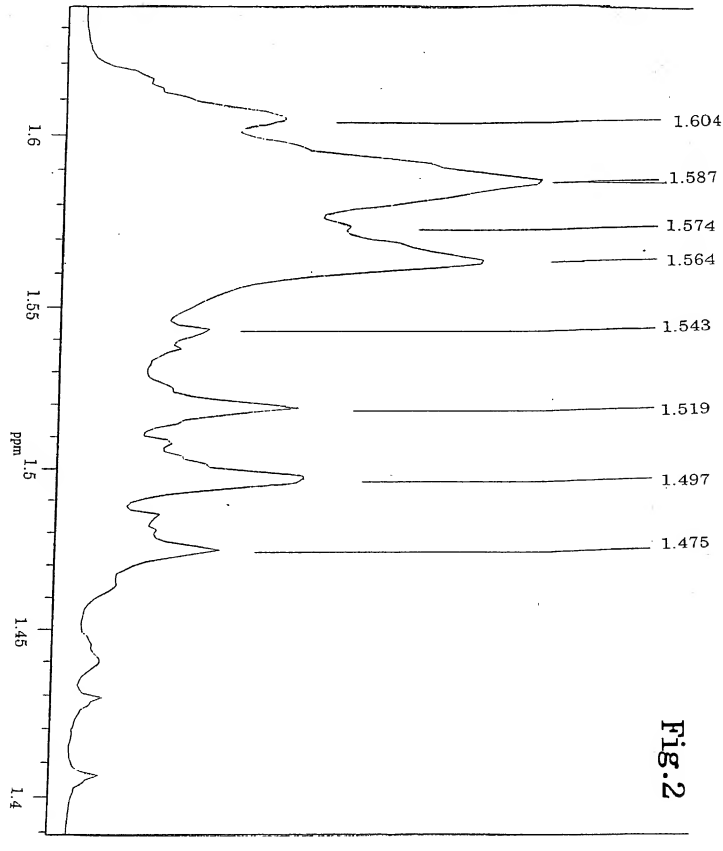


Fig.2

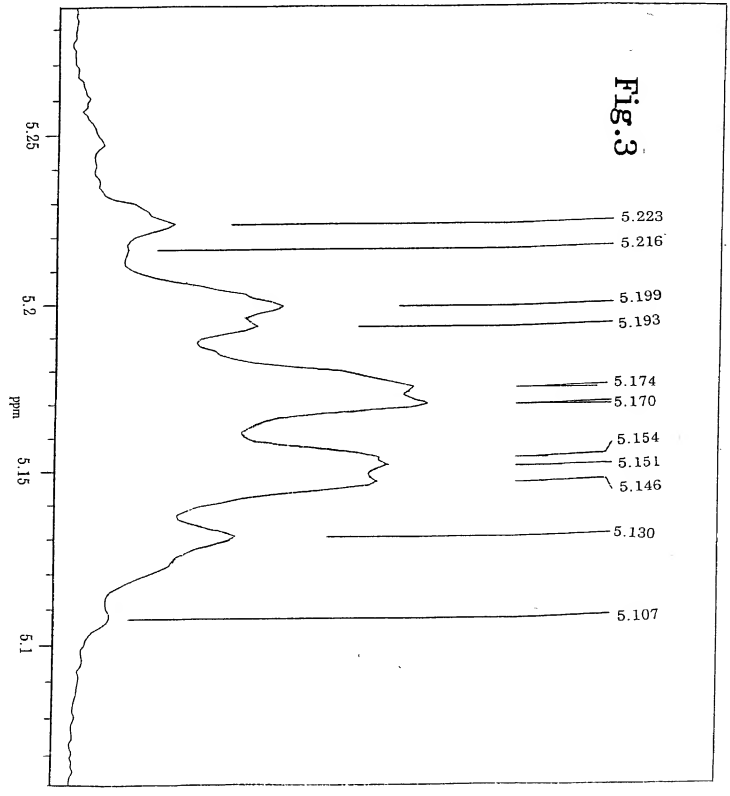


Fig.3

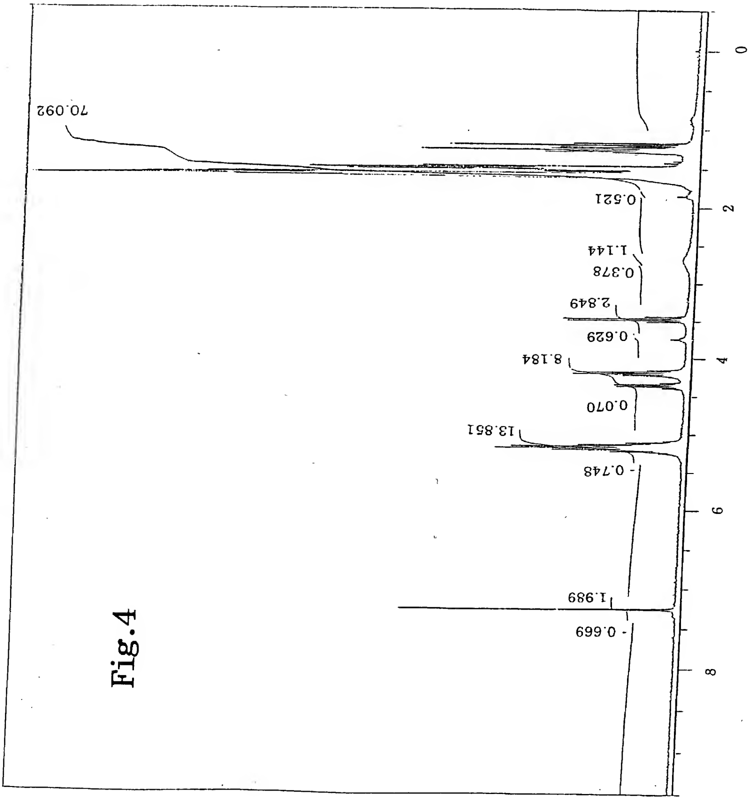


Fig.4

Fig.5

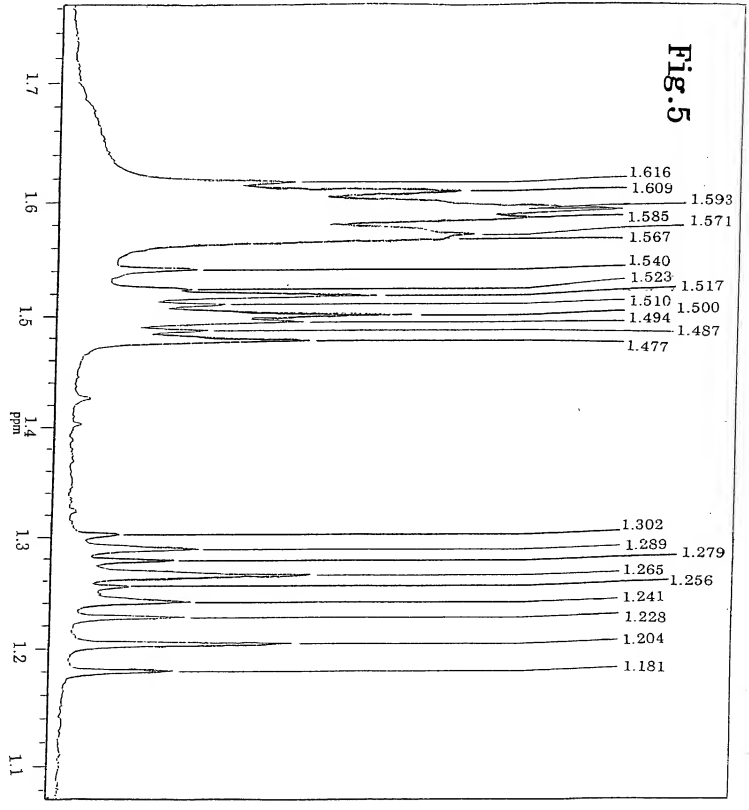
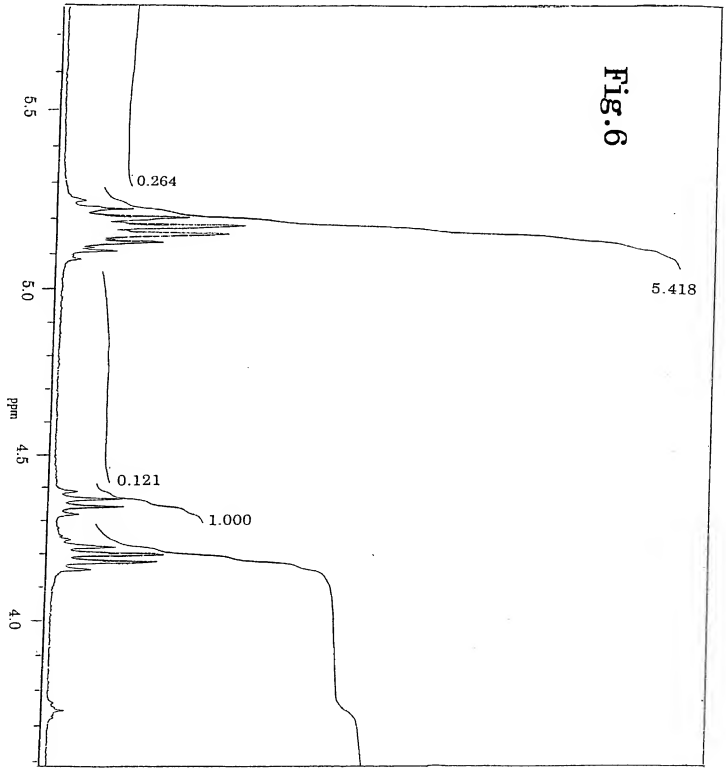


Fig.6



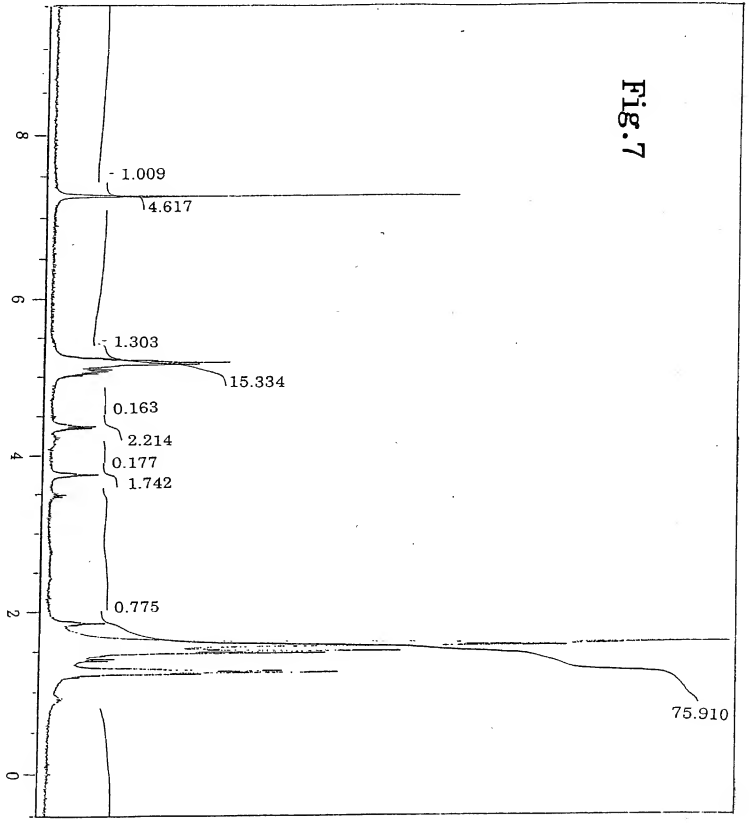


Fig.7

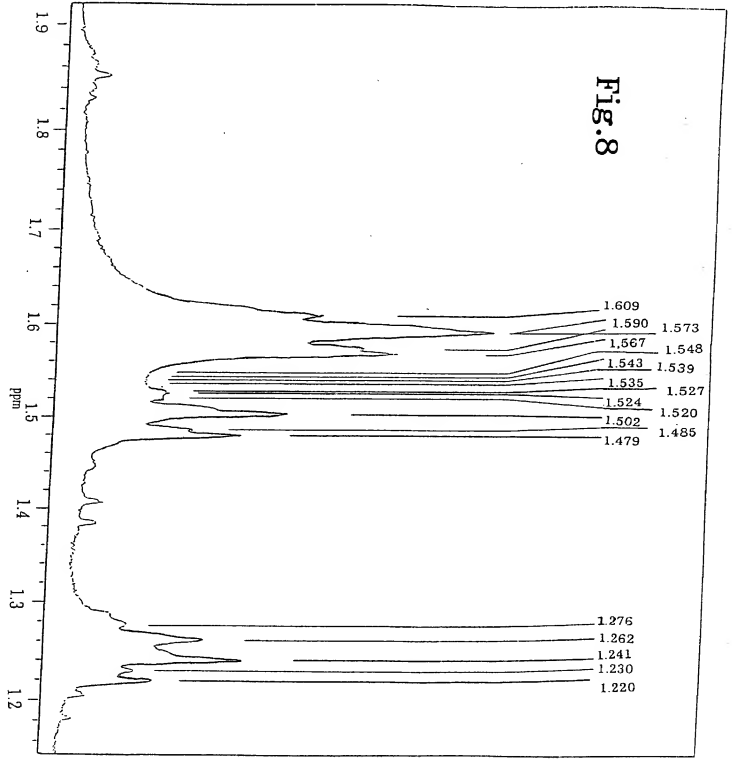


Fig.8

Fig.9

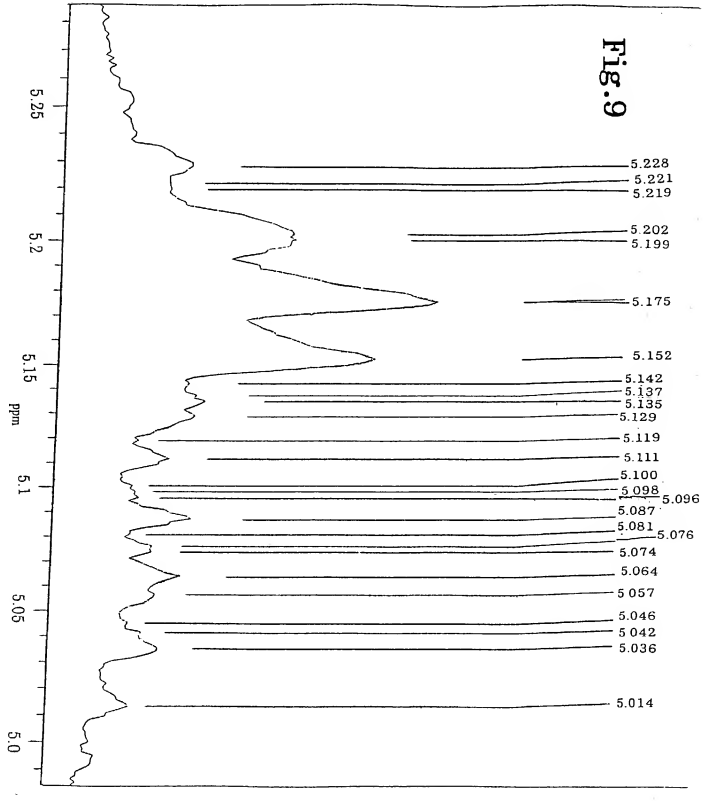


Fig.10

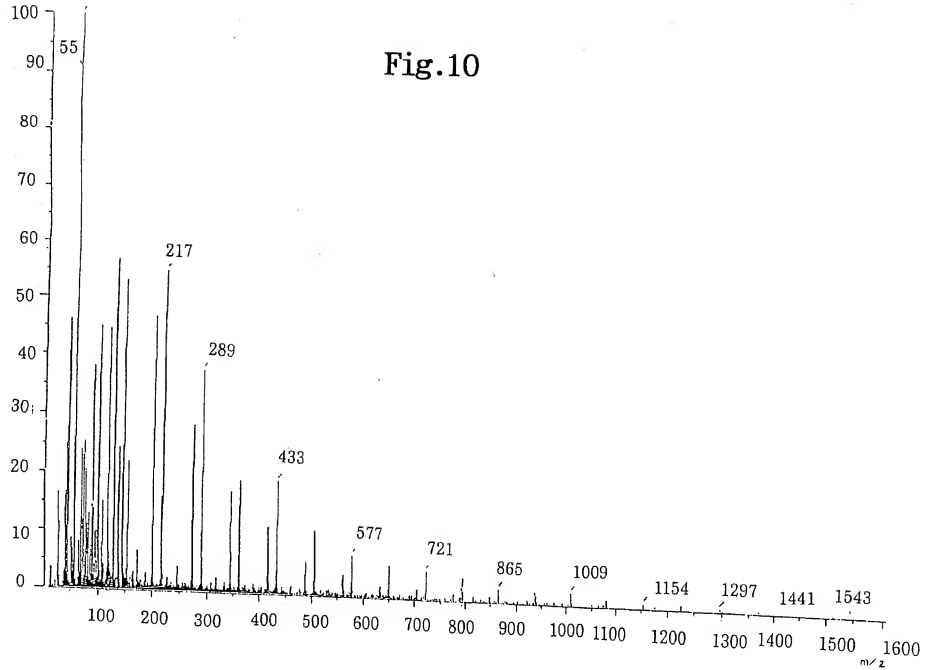
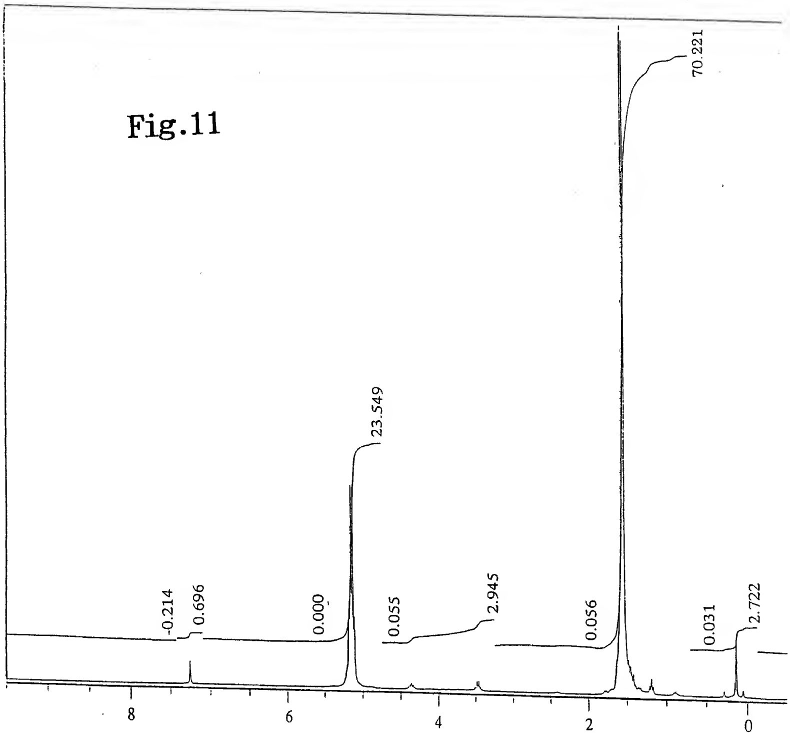


Fig.11



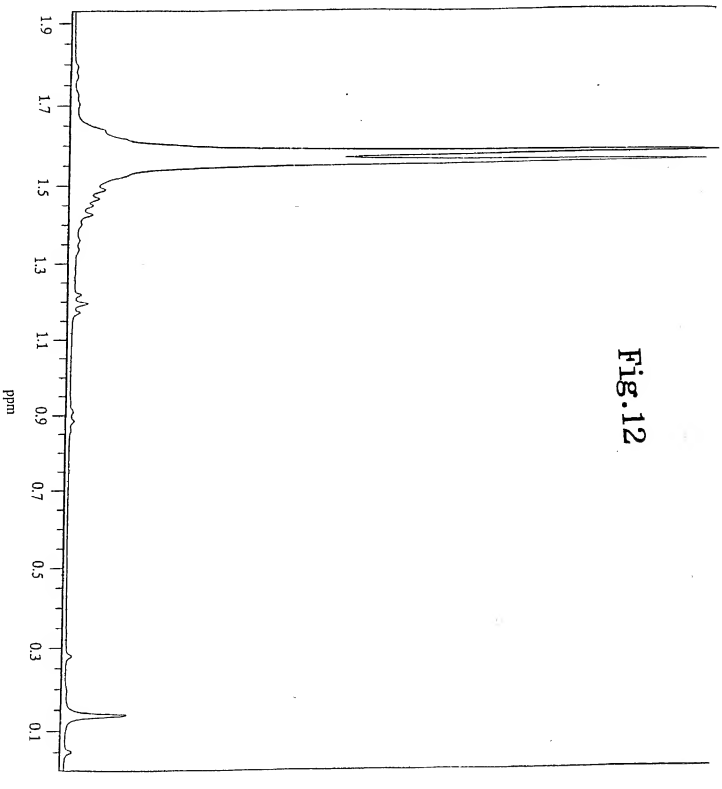


Fig.12

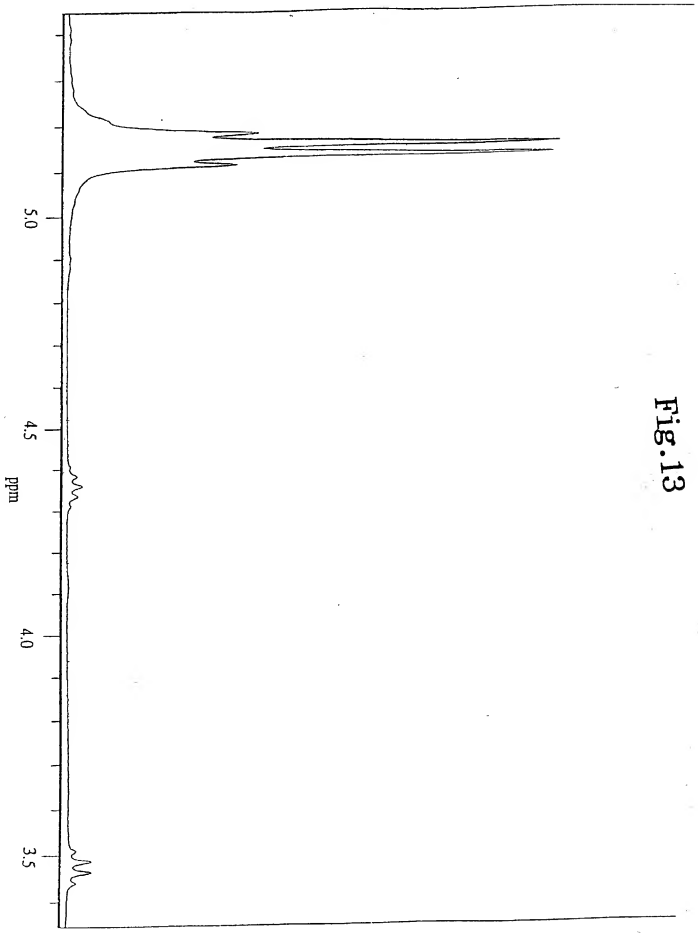


Fig.13

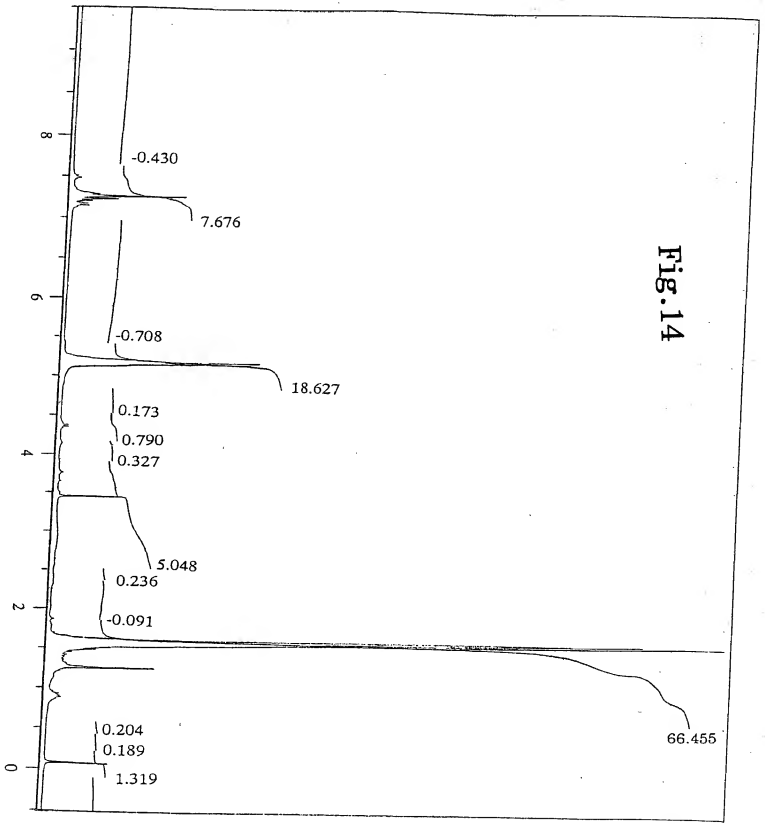


Fig.14

Fig.15

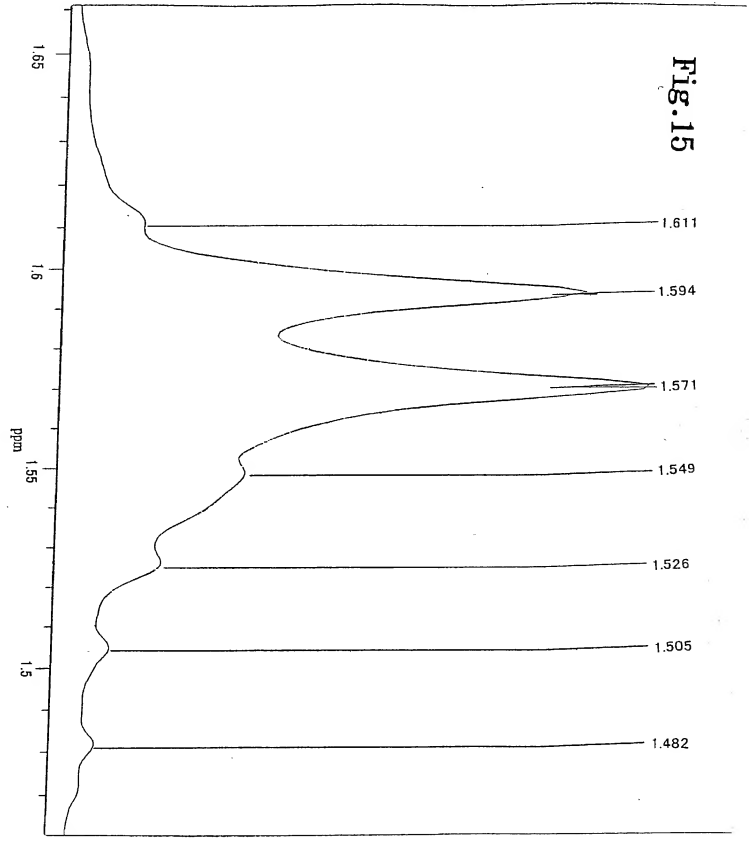
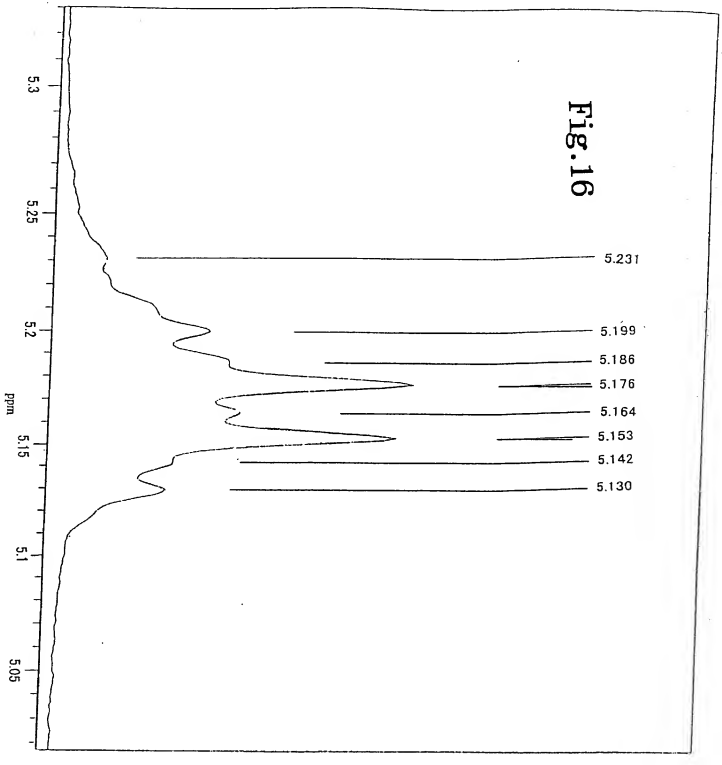


Fig.16



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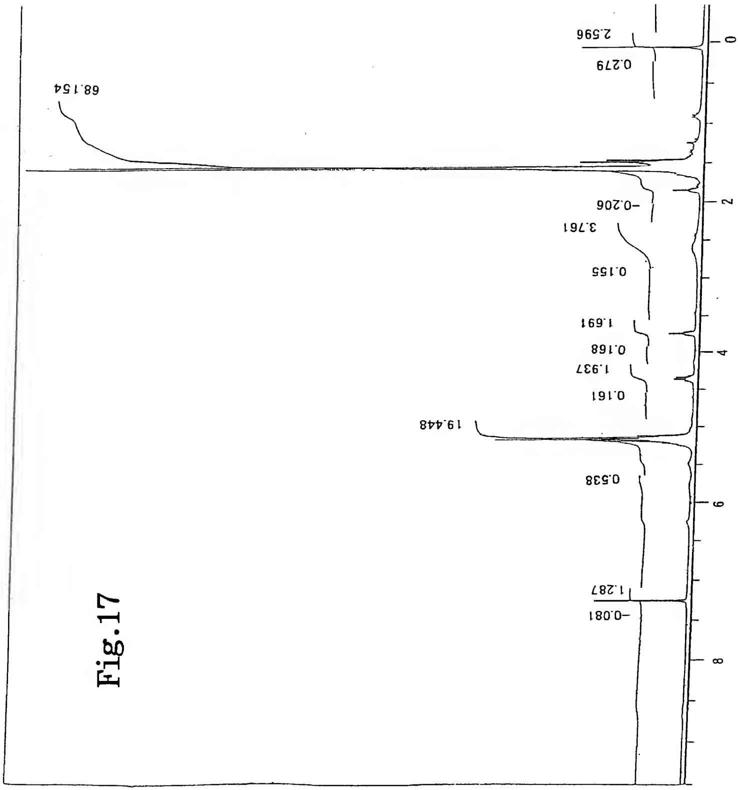

Fig.17

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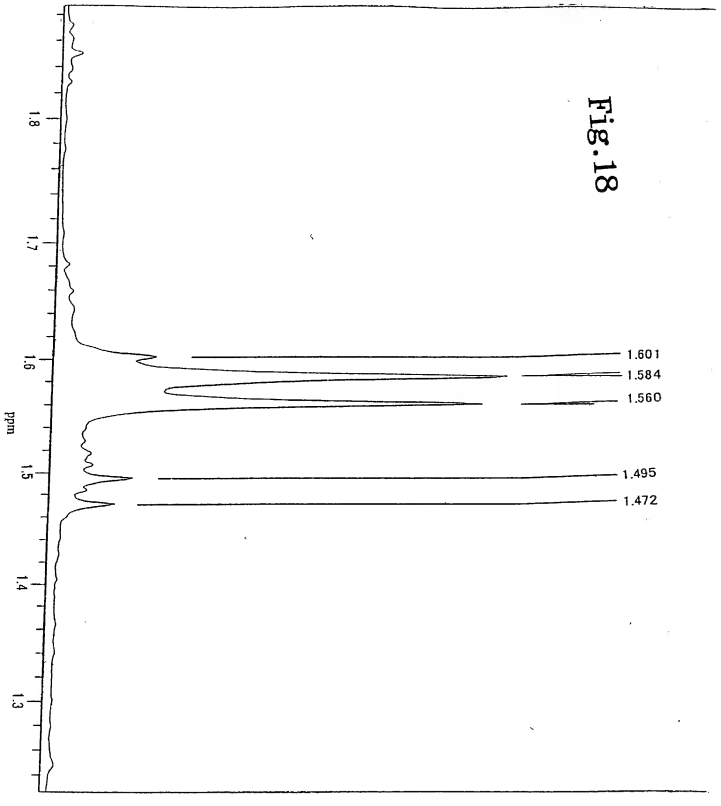
Fig.18



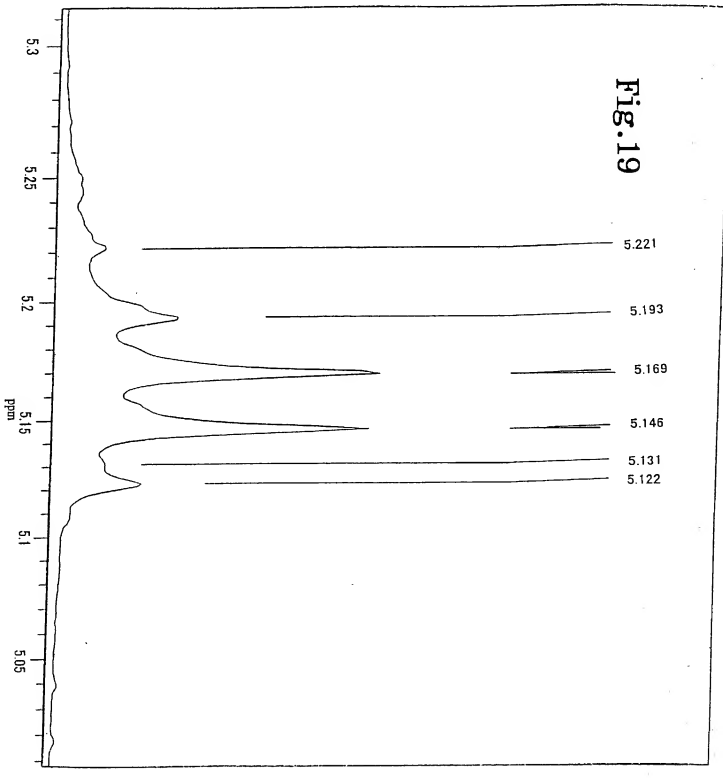


Fig.19

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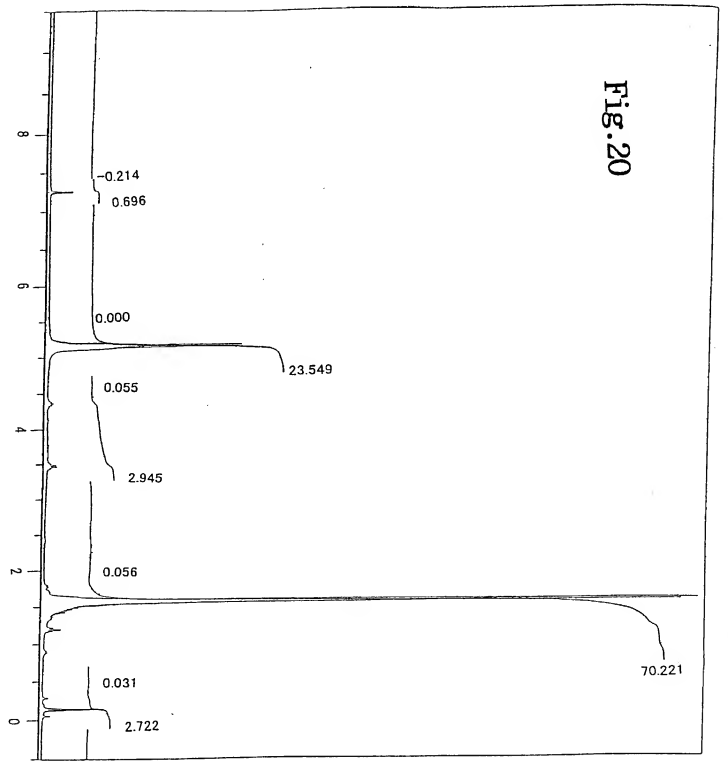
Fig.20



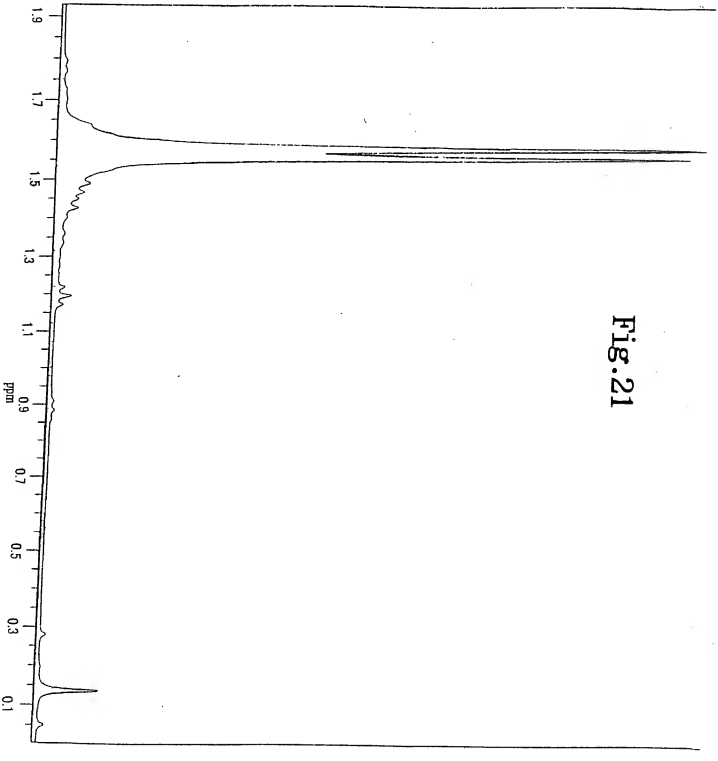


Fig.21

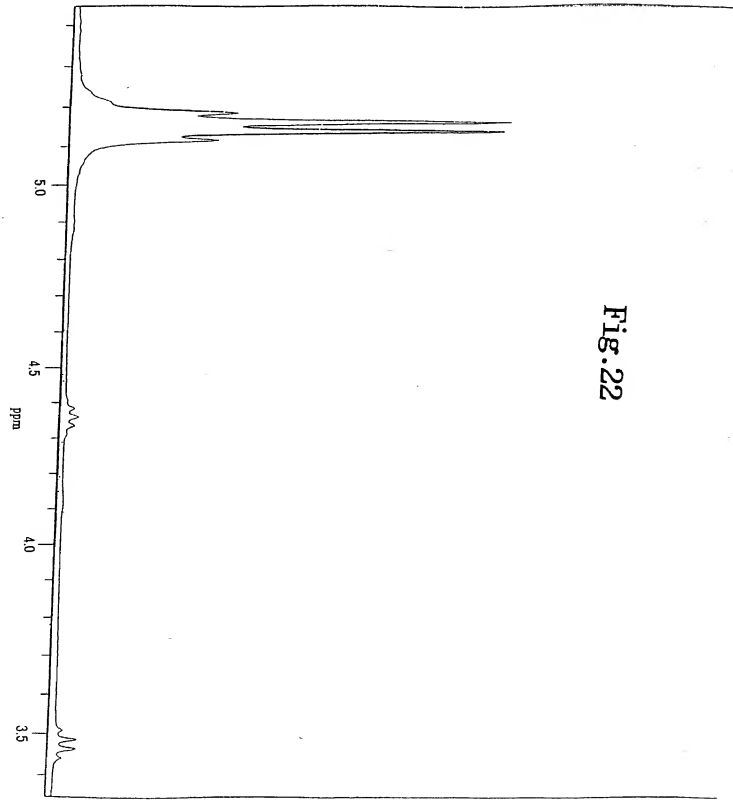


Fig.22

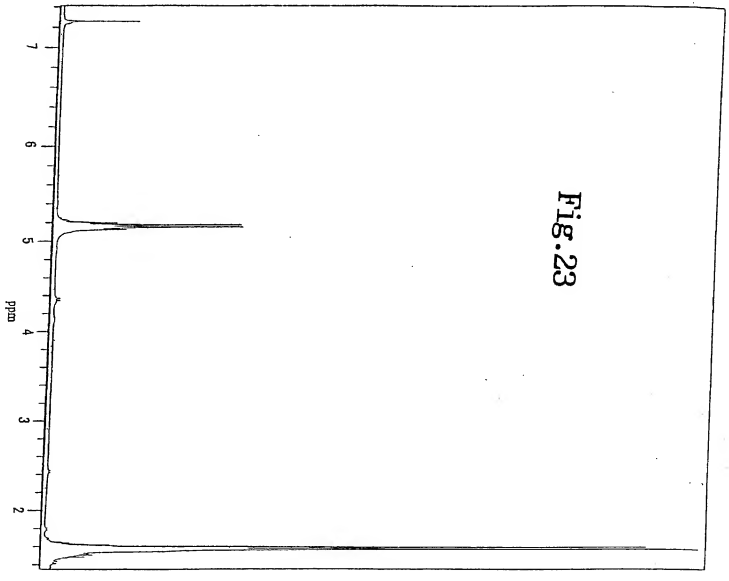


Fig.23

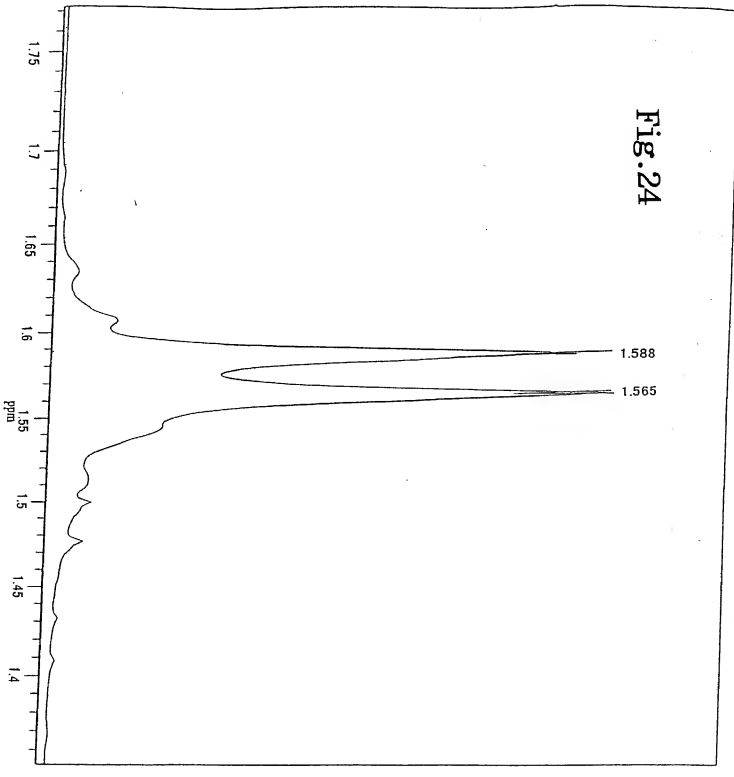


Fig.24

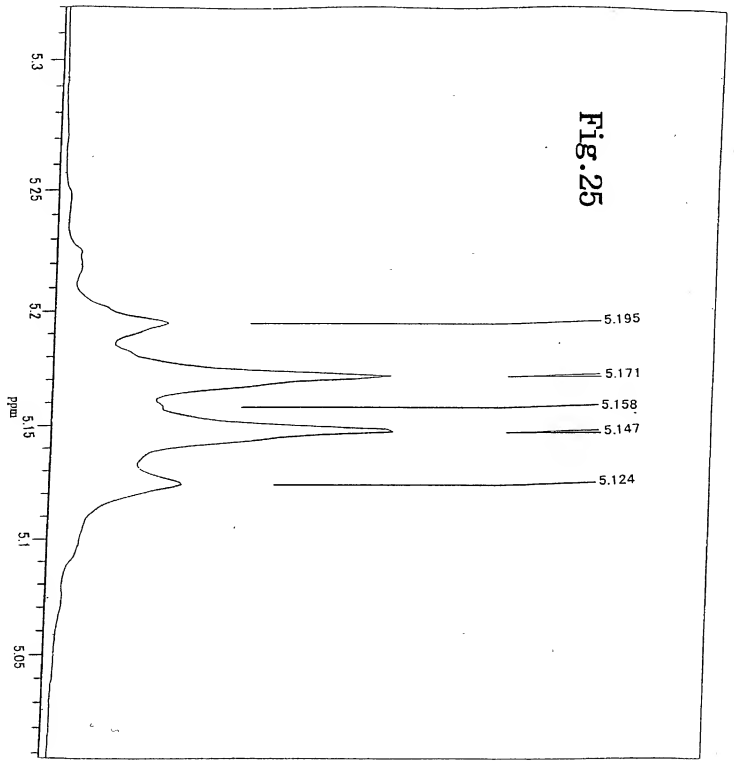


Fig.25

Fig.26

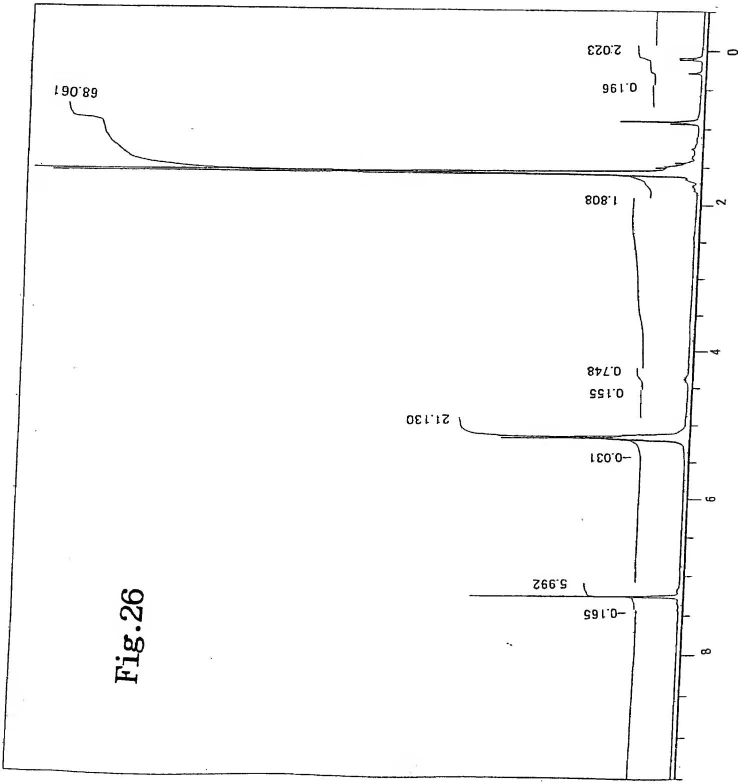


Fig.27

88064
100
50
0
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
m/z
43
55
183
263
355
435
567
675
809
859

Fig.28

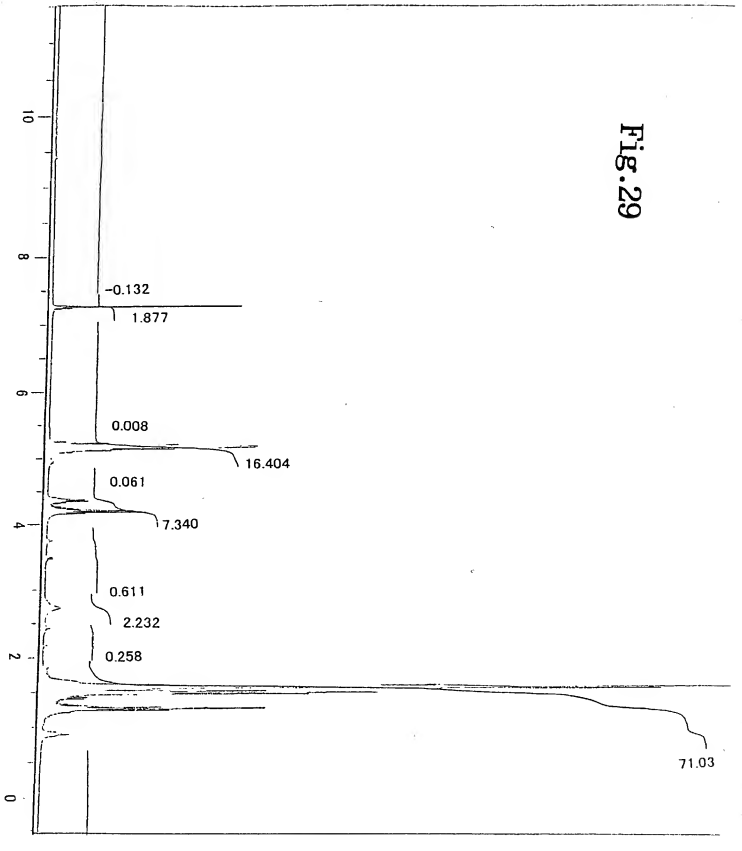
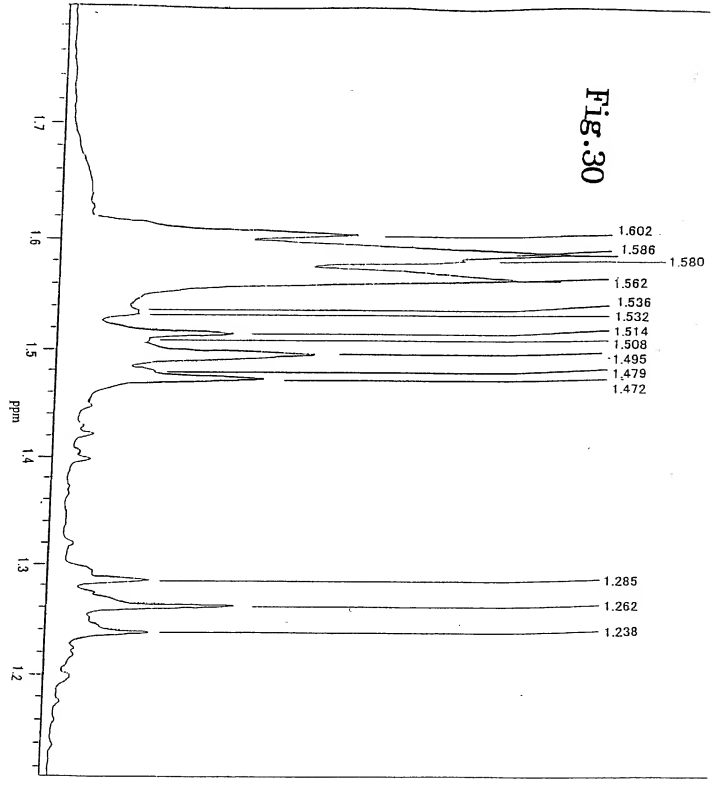


Fig.29

Fig.30



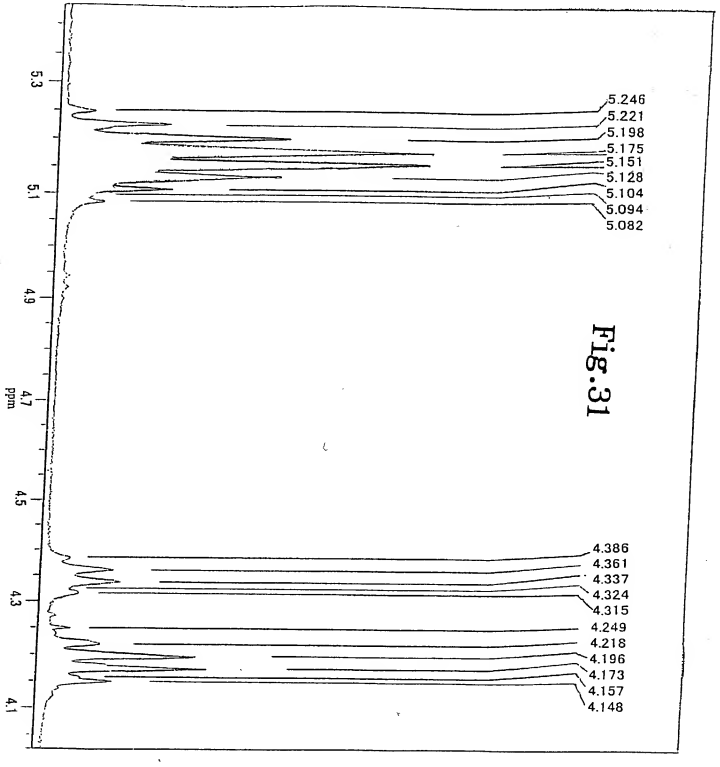


Fig.31

10070436A.656A/US

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Declaration and Power of Attorney for Utility or Design Patent Application
特許出願宣言書

Japanese Language Declaration

私は、下欄に氏名を記載した発明者として、以下のとおり宣言する：

私の住所、郵便の宛先および国籍は、下欄に氏名に続いて記載したとおりであり、

名称の発明に関し、請求の範囲に記載した特許を求める主題の本来の、最初にして唯一の発明者である（一人の氏名のみが下欄に記載されている場合）か、もしくは本来の、最初にして共同の発明者である（複数の氏名が下欄に記載されている場合）と信じ、

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method for Producing Cyclic Lactic Acid Oligomer

上記発明の明細書（下記の欄で X 印がついていない場合は、本書に添付）は、

☐ ____年____月____日に提出され、米国出願番号 _____ とし、（該当する場合）

____年____月____日に訂正されました。又は、

特許協定条約国際出願番号_____とし、

（該当する場合）____年____月____日に訂正されました。

the specification of which is attached hereto unless the following box is checked:

☒ was filed on **20/Sep/00** as United States Application Number **10/070436** and was amended on **19/Mar/02** (if applicable) or,

PCT International Application Number **PCT/JP00/06398** and was amended on _____ (if applicable).

私は、前記のとおり補正した請求の範囲を含む前記明細書の内容を検討し、理解したことを陳述する。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第 37 編第 1 条 56 項に定義されているとおり、特許資格の有無について重要な情報を開示すべき義務があることを認めます。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

私は、合衆国法典第 35 部第 119 条 (a-d) 項又は第 365 条 (b) 項に基づく、下記の外国特許出願又は発明者証出願、或いは第 365 条 (a) 項に基づく、少なくても米国以外の 1 カ国を指名した PCT 国際出願の外国優先権を主張し、更に優先権の主張に係わる基礎出願の出願日前の出願日を有する外国特許出願、又は発明者証出願或るいは PCT 国際出願を以下に "なし" の箱に印をつけることにより明記する：

I hereby claim foreign priority under Title 35, United States Code §119(a-d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States, listed below. I have also identified below, by checking the "No" box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior foreign applications 先の外国出願			Priority claimed 優先権の主張
11-265715 (Number) （番号）	**Japan** (Country) (国名)	**20/Sep/99** (Day/Month/Year Filed) (出願の年月日)	☒ Yes ☐ No あり なし
(Number) （番号）	(Country) (国名)	(Day/Month/Year Filed) (出願の年月日)	☐ Yes ☐ No あり なし

☐ その他の外国特許出願番号は別紙の追補優先権欄にて記載する。

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

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Japanese Language Utility or Design Patent Application Declaration

私は、合衆国法典第 35 部第 119 条(e)項に基づく、下記の合衆国仮特許出願の利益を主張する。

(Application No.)
(出願番号)

(Application No.)
(出願番号)

(Application No)
(出願番号)

☐ その他の合衆国仮特許出願番号は別紙の追補優先権欄にて記載する。

私は、合衆国法典第 35 部第 120 条に基づく下記の合衆国特許出願、又は第 365 条(c)項に基づく合衆国を指名した PCT 国際出願の利益を主張し、本願の請求の範囲各項に記載の主題が合衆国法典第 35 部第 112 条第 1 項規定の態様で、先の合衆国特許出願又は PCT 国際出願に開示されていない限度において、先の出願の出願日と本願の国内出願日又は PCT 国際出願日の間に有効となった連邦規則法典第 37 部第 1 章第 56 条に記載の特許要件に所要の情報を開示すべき義務を有することを認める。

(Application No.)
(出願番号)

(Day/Month/Year Filed)
(出願の年月日)

(Application No.)
(出願番号)

(Day/Month/Year Filed)
(出願の年月日)

☐ その他の合衆国又は国際特許出願番号は別紙の追補優先権欄にて記載する。

私は、ここに自己のに知識に基づいて行った陳述が全て真実であり、自己の有する情報および信ずるところに従って行った陳述が真実であると信じ、さらに故意に虚偽の陳述等を行った場合、合衆国法典第 18 部第 1001 条により、罰金もしくは禁　に処せられるか、またはこれらの刑が併科され、またかかる故意による虚偽による陳述が本願ないし本願に対して付与される特許の有効性を損なうことがあることを認識して、以上の陳述を行ったことを宣言する。

私、下記署名者は、ここに記載の米国弁護士または代理人に本出願に関し特許商標庁にて取られるいかなる行為に関して、同米国弁護士又は代理人が私に直接連絡なしに私の外国弁護士或るいは法人代表者からの指示を受け取り、それに従うようここに委任する。この指示を出す者が変更の場合には、ここに記載の米国弁護士又は代理人にその旨通知される。

I hereby claim the benefit under Title 35, United States Code §119 (e) of any United States provisional application(s) listed below.

(Day/Month/Year Filed)
(出願の年月日)

(Day/Month/Year Filed)
(出願の年月日)

(Day/Month/Year Filed)
(出願の年月日)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(現況)
(特許済み、係属中　放棄済み)

(Status)
(patented, pending, abandoned)

(現況)
(特許済み、係属中　放棄済み)

(Status)
(patented, pending, abandoned)

☐ Additional U.S. or international application numbers are listed on a supplemental priority sheet attached hereto.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from either his foreign patent agent or corporate representative, if any, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

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Japanese Language Utility or Design Patent Application Declaration

委任状：　私は、下記発明者として、下記に明記された顧客番号を伴う以下の弁護士又は、代理人をここに選任し、本願の手続きを遂行すること並びにこれに関する一切の行為を特許商標庁に対して行うことを委任する。そして全ての通信はこの顧客番号宛に発送される。

顧客番号　7055

現在委任された弁護士は下記の通りである。

POWER OF ATTORNEY: As a named inventor, I hereby appoint the attorney(s) and/or agent(s) associated with the Customer Number provided below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

CUSTOMER NUMBER 7055

The appointed attorneys presently include:

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同第二共同発明者の署名　日付	Second Inventor's signature　Date [signature]　June 3, 2002
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国籍	Citizenship Japan
郵便の宛先	Post Office Address 1107-11, Shibusawa, Hadano-shi, Kanagawa 259-1322
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（第三またはそれ以降の共同発明者に対しても同様な情報および署名を提供すること。）

(Supply similar information and signature for third and subsequent joint inventors.)

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Japanese Language Utility or Design Patent Application Declaration

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共同発明者の署名 日付	Fourth Inventor's signature Date June 3, 2002
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国籍	Citizenship Japan
郵便の宛先	Post Office Address 17-6, Kirennishi 3-chome, Hirano-ku, Osaka-shi, Osaka 547-0026 Japan
第五の共同発明者の氏名（該当する場合）	Full name of fifth joint inventor, if any
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国籍	Citizenship
郵便の宛先	Post Office Address
第六の共同発明者の氏名（該当する場合）	Full name of sixth joint inventor, if any
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住所	Residence
国籍	Citizenship
郵便の宛先	Post Office Address

（それ以降の共同発明者に対しても同様な情報および署名を提供すること。）

(Supply similar information and signature for subsequent joint inventors.)